ELSEVIER

Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1999, Vol. 23, pp. 571–588
Published by Elsevier Science Inc.
Printed in the USA.
0278-5846/99/$–see front matter

PII S0278-5846(99)00017-2

DEVELOPMENT OF THE HUMAN CORPUS CALLOSUM DURING CHILDHOOD AND ADOLESCENCE: A LONGITUDINAL MRI STUDY

JAY N. GIEDD, JONATHAN BLUMENTHAL, NEAL O. JEFFRIES, JAGATH C. RAJAPAKSE, A. CATHERINE VAITUZIS, HONG LIU, YOLANDA C. BERRY, MAUREEN TOBIN, JEAN NELSON, and F. XAVIER CASTELLANOS

Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD. USA

(Final form, February 1999)

Abstract

Giedd, Jay N., Jonathan Blumenthal, Neal O. Jeffries, Jagath C. Rajapakse, A. Catherine Vaituzis, Hong Liu, Yolanda C. Berry, Maureen Tobin, Jean Nelson, and F. Xavier Castellanos: Development of the human corpus callosum during childhood and adolescence: A longitudinal MRI study. Prog. Neuro-Psychoparmacol & Biol. Psychiat. 1999, 23, pp. 571–588. Published by Elsevier Science Inc.

1. Interest in the morphologic development of the corpus callosum (CC) during childhood and adolescence stems from adolescent changes in cognitive functions subserved by the CC, reports of CC anomalies for a wide variety of childhood neuropsychiatric illnesses, and controversy regarding sexual dimorphism.
2. Characterization of the normal developmental pattern of the CC is hindered by enormous variability of its size. This is especially problematic for cross-sectional studies seeking to assess possible non-linear developmental curves.
3. To more accurately characterize developmental changes, a longitudinal brain magnetic resonance imaging study with subjects rescanned at approximately 2 year intervals was conducted resulting in 251 scans from 139 healthy children and adolescents.
4. Midsagittal area of the CC, especially the posterior regions, increased robustly from ages 5 to 18 years.
5. Although the genu of the CC was significantly larger in males there were no sex differences in mean area after adjustment for total cerebral volume and the growth patterns did not differ between sexes.
6. Analysis revealed a non-linear increase in the splenium, the most posterior region, with increases greatest in the younger years.
7. The results of this longitudinal study, in addition to confirming and extending previous cross-sectional reports, provide an increasingly accurate yardstick from which to assess pathological development.

Keywords: adolescent, brain, child, sex

Abbreviations: corpus callosum (CC), intraclass correlation coefficient (ICC), magnetic resonance imaging (MRI)

Introduction

The corpus callosum (CC) is the main interhemispheric commissure of the brain, consisting of approximately 180 million mostly myelinated axons which connect homologous areas of the left and right cerebral cortex (Tomasch, 1954). Although notably absent in monotrenes and marsupials, the CC is present in most animals from insectivores to higher primates and appears to have evolved in parallel with the neocortex (Kappers et al., 1936; Rapoport, 1990). The fibers coursing through the CC generally take the shortest route and therefore roughly maintain a topographic pattern with the anterior sections consisting of fibers connecting frontal brain areas, middle sections connecting middle cortical areas, and posterior sections connecting posterior cortical areas. There is some controversy about how tightly the spatial relationships of the cortex are maintained in their CC representation but for some of the areas studied, such as the somatosensory regions, the spatial representation is highly preserved (Innocenti et al., 1974; Spidalieri et al., 1985).

In general, the CC functions to integrate the activities of the left and right cerebral hemispheres. This includes organizing bimanual motor output (Zaidel and Sperry, 1977) and unifying the sensory fields (Berlucchi, 1981; Shanks et al., 1975). The CC is also involved in memory storage and retrieval (Zaidel and Sperry, 1974), attention and arousal (Levy, 1985), language and auditory functions (Cook, 1986), and maybe in the perception of consciousness (Joseph, 1980). Creativity and intelligence are linked to interhemispheric integration (Bogen and Bogen, 1969) and the more difficult the cognitive task the more critical interhemispheric integration becomes (Hellige et al., 1979; Levy and Trevarthen, 1981). These capacities subserved by the CC continue to improve during childhood and adolescence highlighting interest in the structural characteristics of the CC during this developmental time period. Structural changes have been shown to progress throughout childhood and adolescence (Giedd et al., 1996a) and anomalies of CC morphology have been reported for several neuropsychiatric disorders of childhood (Bigelow et al., 1983; Giedd et al., 1994; Hynd et al., 1990; Hynd et al., 1991; Njiokiktjien, 1991; Parashos et al., 1995; Peterson et al., 1994; Rosenthal and Bigelow, 1972).

The CC is noteworthy as one of the first brain structures not directly related to reproduction that was reported in post-mortem samples to demonstrate sexual dimorphism (de Lacoste-Utamsing and Holloway, 1982). Subsequent MRI studies have been inconsistent with some studies reporting sex differences (Clarke et al., 1989; Cowell et al., 1992; de Lacoste et al., 1986), but more not finding such differences (Bell and Variend, 1985; Byne et al., 1988; Oppenheim et al., 1987; Weis et al., 1988; Weis et al., 1989;

Witelson, 1985a; Witelson, 1985b). Surprisingly, few of these studies addressed the effects of age on CC morphology. The discrepancies regarding sexual dimorphism of the CC may be related to differences in measurement technique, MRI acquisition, subject selection, or not taking into account differences in CC growth patterns between adult men and women (Cowell et al., 1992).

In a previous cross-sectional study, the authors reported age-related, but not sex-related changes, in CC morphology in a group of 114 healthy children and adolescents (Giedd et al., 1996a). A striking feature of the data was the enormous variability in CC size. The high variability makes it difficult to characterize heterochronous (non-linear) developmental changes. To more accurately capture developmental changes we embarked upon a longitudinal study to rescan children and adolescents at approximately two-year intervals. This study reports the effects of age and sex on CC morphology in healthy children and adolescents using longitudinal imaging data.

Methods

Subjects

Subjects were recruited from the community and screened in a three-part process. The initial step consisted of a telephone interview in which parents were asked about their child's current functioning, use of medication, or special service needs in school. Approximately one-third of the subjects were excluded during this process. To those not excluded by the telephone screening the Child Behavior Checklist (Achenbach and Edelbrock, 1983) and Conners Parent Questionnaire (Conners, 1973) were mailed to the parents and the Conners Teacher Questionnaires (Goyette et al., 1978) was mailed to the child's teacher. Approximately one-half of the remaining subjects were excluded based on the results of these questionnaires. The remaining group was then evaluated at the NIH clinical center. Assessment included a physical and neurological examination, a structured psychiatric interview using the Child and Parent Diagnostic Interview for Children - Revised (Welner et al., 1987), the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children - Revised (WISC-R; Wechsler, 1974), and a clinical interview of the subject and parent(s) by a child and adolescent psychiatrist (JNG) which included a family history assessment. Approximately one-half of the subjects who had physical, neurological, or current/lifetime history of psychiatric abnormalities, or who had first degree relatives with major psychiatric disorders were excluded at this stage. The demographics of the subjects accepted for the study are presented in Table 1. All subjects were assessed by the 12 Handedness items from the

Physical and Neurological Examination for Subtle Signs (PANESS) inventory (Denckla, 1985). The protocol was approved by the Institutional Review Board of the National Institute of Mental Health. Assent from the child and written consent from the parents were obtained.

Table 1

Characteristics of Healthy MRI Subjects (N = 139) at Time of Initial Scan

	Male (N = 85)		Female (N = 54)[a]	
	Mean ± SD	Range	Mean ± SD	Range
Age (years)	10.3 ± 3.8	4.4-17.8	11.3 ± 3.8	4.6-18.3
Height (inches)	57.1 ± 8.9	38.0-75.5	58.4 ± 8.0	41-71
Weight (pounds)	88.1 ± 37.1	32-175	94.4 ± 35.7	39-180
Tanner stage	2.1 ± 1.5	1-5	2.4 ± 1.6	1-5
Handedness (% right)	89		86	

[a] No statistical differences between sexes on any of these variables.

MRI Protocol

All subjects were scanned on the same GE 1.5 Tesla Signa scanner. T1-weighted sagittal images with slice thickness of 1.5 mm in the axial and sagittal planes and 2.0 mm in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state (3D SPGR). Imaging parameters were time to echo = 5 msec, time to repeat = 24 msec, flip angle = 45 degrees, acquisition matrix = 192 x 256, number of excitations =1, and field of view = 24 cm. Vitamin E capsules, wrapped in gauze and placed in the meatus of each ear, were used to help standardize head placement. A third capsule was taped to the lateral aspect of the left inferior orbital ridge. The vitamin E capsules are readily identifiable with our scanning parameters, and the three capsules were used to define a reference plane for our images. The patient's head was aligned in a head holder so that a narrow guide light passed through each of the vitamin E capsules. Foam padding was placed on both sides of the patient's head to minimize head movement. A sagittal localizing plane was acquired, and from this, a multi-echo axial series to assure that one of the axial slices contained all three of the capsules. If no slice clearly contained all three capsules, the patient was realigned until this criterion was met. An additional criterion, to control for tilt within the coronal plane, was the alignment of each subject's nose at the "12:00" position. It should be

noted that these alignment criteria were based on external landmarks only and did not guarantee standardization of internal structures.

Subjects were scanned in the evening to promote falling asleep in the scanner. Younger children were allowed to bring blankets or stuffed animals into the scanner and have their parents read to them. Nine children who had been accepted for the study were unable to complete the scan due to claustrophobia or excessive anxiety. No sedation was used. Seventy-five of the children (51 boys, 24 girls) were scanned a second time (mean interval 2.3 years), 34 of the children (25 boys, 9 girls) were scanned a third time (mean interval 2.01 years), and 3 of the children (1 boy, 2 girls) were scanned a fourth time (mean interval 2.35 years). The total number of scans was 251.

Image Analysis

All scans were evaluated by a clinical neuroradiologist. Two subjects were noted to have areas of increased T2 signal intensity; one in the left semiovale and one in the right parietal lobe. Both subjects were retained in the data set. Images were transferred to a Macintosh II FX computer workstation and analyzed with an image analysis program (Image 1.46) developed at the NIH (Rasband, 1993).

CC Quantification. The CC, because of the orientation and extensive myelination of its fibers sharply contrasts its neighboring gray matter and cerebrospinal fluid tissue and is therefore easily visualized on both magnetic resonance images (MRI) and postmortem exam. The most reliable estimate of size is derived from the midsagittal measure (Malobabic et al., 1985), but precise determination of this plane is crucial because the CC fans out quickly from the midsagittal plane and slight errors to the either side can lead to erroneously high measures. To accurately capture the midsagittal plane a line was drawn to bisect the cerebral hemispheres from the axial 3D data set at the level of the anterior commissure and posterior commissure. From this line, a midsagittal image was reconstructed. Criteria to confirm a midsagittal orientation were patency of the cerebral aqueduct, presence of the septum pellucidum, and distinctness of the thalamus. The images were then rotated in the sagittal plane to a standard orientation based on the anterior and posterior commissures. Non-standard orientation in this plane should not affect the overall size of the midsagittal CC measure but may affect the relative sizes of the subdivisions.

From this midsagittal slice, an elliptical region of interest encompassing the corpus callosum was drawn and within this region a supervised thresholding technique was used to determine the x-y coordinates of

the perimeter of the corpus callosum. All measures were made by the same rater (ACV) who measured all of the scans over a three-month period while blind to the age or gender of the subjects. Twenty scans were randomly entered into the data set to be measured twice to determine intra-rater reliability.

A C language program was written (JCR) to use the x-y coordinates of the perimeter of the corpus callosum to quantify the total and seven subregions of the CC based on a modification of divisions used in postmortem analyses (Witelson, 1989; see Figure 1).

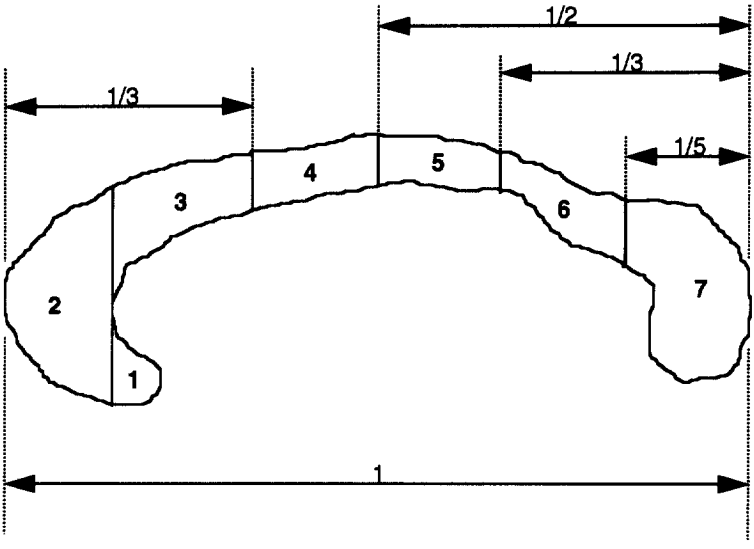

Fig 1. Regional subdivisions of the corpus callosum, adapted from Witelson et al. (1989). Subregions: (1) rostrum, (2) genu, (3) rostral body, (4) anterior midbody, (5) posterior midbody, (6) isthmus, (7) splenium.

Total Cerebral Volume Quantification. To quantify total cerebral volume we used a technique which applied successive iterations of an energy minimization function to enforce constraints on curvature and topology of a mathematically modeled template brain (Snell et al., 1995) allowing prior knowledge of brain anatomy contained in the template to supplement MRI signal intensity characteristics. Each axial

slice of the brain was then edited by experienced raters to remove artifacts such as patches of dura or eyeball. Further details are provided elsewhere (Giedd et al., 1996b).

Statistical Analysis

Intra-rater reliability for the CC measurements was assessed by intraclass correlation (ICC). Differences between males and females on the demographic variables (age, height, weight, handedness) were examined with t tests or chi-square analysis. All p values from statistical tests are two-tailed.

Longitudinal data analysis methods (Diggle et al., 1994) were used to examine growth rates of CC components. The PROC MIXED procedure in the SAS software package (SAS Institute, 1990) was used to perform these analyses. To explore the hypothesis that growth rates of a given CC component might not remain constant with age, quadratic curves were fit to the data (a constant, age, and age^2 were used as covariates in the longitudinal growth models). An equation of this model is Size = Intercept + β_1*Age + β_2*Age^2 + ε.

These models describe non-linear growth and test the hypothesis that quadratic curves fit the data significantly better than the straight lines estimated from models that contain only a constant and age as covariates. These quadratic regression models were mixed in that both fixed and random effects were present. The intercept terms were treated as random effects that varied by individual, while the coefficients for the age and age^2 terms were modeled as fixed. Additionally, a repeated measures structure was employed to model the dependence between measurements on the same individual (the REPEATED option in PROC MIXED was used with TYPE=SP(GAU) (AGESCAN)). Wald and Z statistics were used for hypothesis tests of these models. Rationale for Wald and Z-statistics are discussed in Section 5.3.3 in Diggle et al. (1994).

Results

Measurement Reliability

Intra-rater ICCs for the seven subdivisions of the CC averaged 0.92.

Sex Differences in Mean Area

As indicated in Table 1, there were no significant differences between boys and girls on height, weight, age, Tanner stage, or handedness. As indicated in Table 2, the genu was significantly larger in males and there was a trend for a larger anterior midbody. Total cerebral volume (defined as the sum of gray and white matter in the cerebrum) was approximately 11% larger in males (1046 ml vs. 1174 ml, $t = 7.4$, $p < 0.0001$).When adjusted for total cerebral volume using an ANCOVA there were no significant sex differences in mean area for the total corpus callosum or any of its seven subdivisions although there was a trend for the total, genu, posterior midbody and isthmus to be proportionately larger in females.

Table 2

Adjusted and Unadjusted Sex Differences in Mean Size of CC and Components in Healthy Children and Adolescents at Time of First Scan (N = 139)

	Male	Female	ANOVA		ANCOVA[1]	
Structure	Mean ± SD	Mean ± SD	Male-Female Difference	p value[2]	Adjusted Male-Female Difference	p value[3]
Rostrum	26.9 ± 12.5	24.7 ± 11.2	2.2	0.29	0.5	0.84
Genu	140.1 ± 26.2	130.4 ± 22.2	9.7	0.03	-7.1	0.10
Rostral body	92.0 ± 15.8	91.9 ± 17.2	0.1	0.97	-4.9	0.13
Anterior midbody	71.7 ± 10.6	68.1 ± 10.6	3.6	0.06	-2.0	0.30
Posterior midbody	62.5 ± 11.6	60.7 ±10.7	1.8	0.36	-3.9	0.07
Isthmus	52.0 ± 11.3	51.4 ± 9.4	0.6	0.74	-3.6	0.08
Splenium	163.5 ± 31.2	159.2 ± 25.1	4.3	0.40	-4.6	0.42
Total CC	608.6 ± 82.3	586.4 ± 75.1	22.2	0.11	-25.7	0.07

[1] ANCOVA adjusts by using total cerebral volume as a covariate. [2] t test used to obtain p values. [3] F test used to obtain p values.

Maturational Changes

The total midsagittal cross-sectional area of the CC increases markedly across ages 5 to 18 years. Table 3 gives the coefficients and standard errors for the two intercepts, slope, and quadratic terms in the equation $\text{Size} = \text{Intercept}*\text{Sex} + \beta_1*\text{Age} + \beta_2*\text{Age}^2 + \varepsilon$. This equation constrains the β_1 and β_2 coefficients to be the same for each sex. The initial forms of the quadratic models allowed for different curves for each sex. In no cases were the curves found to differ between sexes (i.e., the coefficients for age and age^2 for boys and girls were not statistically different) but the height of the curves (as measured

by different coefficients for the intercept term) were sometimes different (anterior midbody, posterior midbody, and CC total). Consequently, a model that has an Intercept*Sex interaction is presented. The interpretation of these patterns is that sometimes the boys had larger CC components, but the growth patterns were the same for both sexes.

Table 3 gives p-values for two hypotheses of interest. The first hypothesis addresses the question of whether there is evidence of any growth, either linear or quadratic. In terms of the equation above, this is a test of whether the β_1 and β_2 coefficients are simultaneously 0. A Wald test statistic (having a χ^2 distribution with 2 degrees of freedom) was used to obtain p-values for this hypothesis. A related, but different question is if there is growth, is it non-linear (i.e., is the β_2 not equal to zero). A Z-statistic (the β_2 coefficient divided by its standard error) is used to obtain p-values for this hypothesis.

Table 3

Estimated Coefficients of Model Size = Intercept*Sex + β_1*Age + β_2*Age^2 + ε for the Total and Seven Subdivisions of the Midsagittal Cross-Sectional Area of the Corpus Callosum for 251 Scans from 139 Subjects Aged 5 To 18 Years.

Structure	Male Intercept	Female[1] Intercept	Age Coefficient β_1 (mm^2/year)	Age^2 Coefficient β_2	p value for β_1=0 & β_2=0	p value for β_2 = 0
Rostrum	24.9 ± 4.8	21.9 ± 5.1	0.05 ± 0.8	.01 ± 0.03	0.94	0.72
Genu	132.0 ± 9.2	121.9 ± 9.7	0.88 ± 1.5	-.01 ± 0.06	0.56	0.90
Rostral body	86.5 ± 6.6	85.0 ± 7.0	0.32 ± 1.1	.02 ± 0.05	0.75	0.67
Anterior midbody	58.7 ± 4.3	54.1 ± 4.4	1.41 ± 0.7	-.01 ± 0.03	0.05	0.65
Posterior midbody	43.0 ± 4.9	39.4 ± 5.1	2.20 ± 0.9	-.03 ± 0.04	0.01	0.46
Isthmus	37.7 ± 3.5	35.6 ± 3.7	1.66 ± 0.6	-.02 ± 0.02	0.004	0.20
Splenium	114.9 ± 7.5	106.7 ± 8.0	6.06 ± 1.2	-.12 ± 0.05	< 0.0001	0.01
Total CC	505.5 ± 23.5	473.5 ± 25.0	11.3 ± 3.8	-.11 ± 0.15	0.002	0.47

[1] Different estimates of the intercept terms were made for each sex. The intercepts were significantly different (Wald test, $p < .05$) for the anterior midbody, posterior midbody, and total CC size. Values are given as means ± the standard errors of the estimated coefficients.

As indicated by Table 3 the increases follow an anterior-to-posterior gradient with no significant changes in the three anterior regions (p = 0. 94, 0. 56, and 0.75 for the rostrum, genu, and rostral body,

respectively), moderate changes in the middle regions ($p = 0.05$ and 0.01 for the anterior midbody and posterior midbody, respectively), and robust changes in the posterior regions ($p = 0.004$ and 0.0001 for the isthmus and splenium, respectively). When the quadratic coefficient, β_2, is not significant, as is the case for all but the splenium, β_1 approximates the amount of change per year (mm^2/year). Figures 2, 3, and 4 provide scatterplots of area by age for the total, genu, and splenium.

Discussion

CC size continues to increase throughout adolescence, particularly in posterior regions. As electron microscopy studies in the rhesus monkey suggest no postnatal development of callosal axons (LaMantia and Rakic, 1984), the most likely explanation for the increased size is an increase in the amount of myelination. The relationship between increased myelination and improved cognitive capacity is conjectured but remains unproven. CC axons in adults are almost all myelinated, varying in size from 0.08 microns to greater than 5 microns with conduction velocities ranging from 1 m/sec to 10 m/sec (Fleischhauer and Wartenberg, 1967; Waxman and Swadlow, 1976). Cell death or axonal retraction may serve to offset the myelination-related increase during development (Clarke et al., 1989; Innocenti, 1981a; Innocenti, 1981b; Innocenti and Caminiti, 1980). An enriched environment has been reported to increase the size of the CC in rats (Juraska and Kopcik, 1988) while hormones, nutrition, and other external factors such as infections, toxins, trauma, or stress may also influence CC size but quantification of these effects are not well characterized.

Reports of clinical differences in CC size have been marred by inconsistency. For instance, for attention-deficit/hyperactivity disorder (ADHD) the CC has been reported to be smaller in anterior regions only (Baumgardner et al., 1996; Giedd et al., 1994), posterior regions only (Semrud-Clikeman et al., 1994), anterior and posterior regions (Hynd et al., 1991), and not different (Castellanos et al., 1996). Likewise, for schizophrenia, the CC has been reported to be larger (Jacobsen et al., 1997), smaller (Nasrallah et al., 1997), and not different (Andreasen et al., 1994). These discrepancies may be related to differences in selections of clinical and/or comparison subjects, image acquisition, or image analysis and also probably reflect errors of small sample studies of highly variable measures.

The predominantly posterior increases in CC size during childhood and adolescence may reflect an earlier maturation of anterior regions or a more pronounced development of interhemispheric connections of posterior regions, such as association areas, during this developmental period.

Conclusion

This large sample longitudinal pediatric study, in addition to supporting an earlier cross-sectional report demonstrating changes in midsagittal CC area throughout childhood and adolescence, provided greater statistical power to examine non-linear developmental patterns and showed non-linear changes in the splenium with more rapid growth at younger ages. Sex differences are subtle and depend on whether adjustments are made for the approximately 11% difference in total cerebral volume. The extremely high variability of the size of the CC during development highlights a need for further longitudinal data collection to adequately characterize healthy developmental patterns and to establish a normative yardstick from which clinical populations may be assessed.

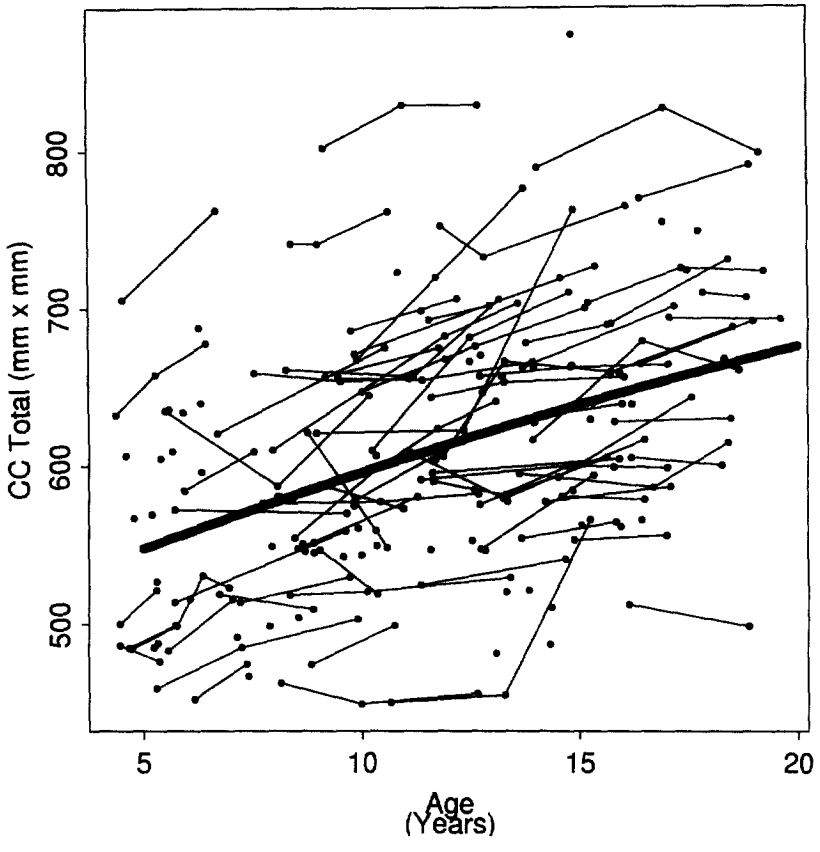

Fig 2. Scatterplots, with longitudinal data points connected by a line, of total midsagittal corpus callosum area (mm^2) vs age (years) for 251 scans from 139 healthy subjects ages 5 - 18 years.

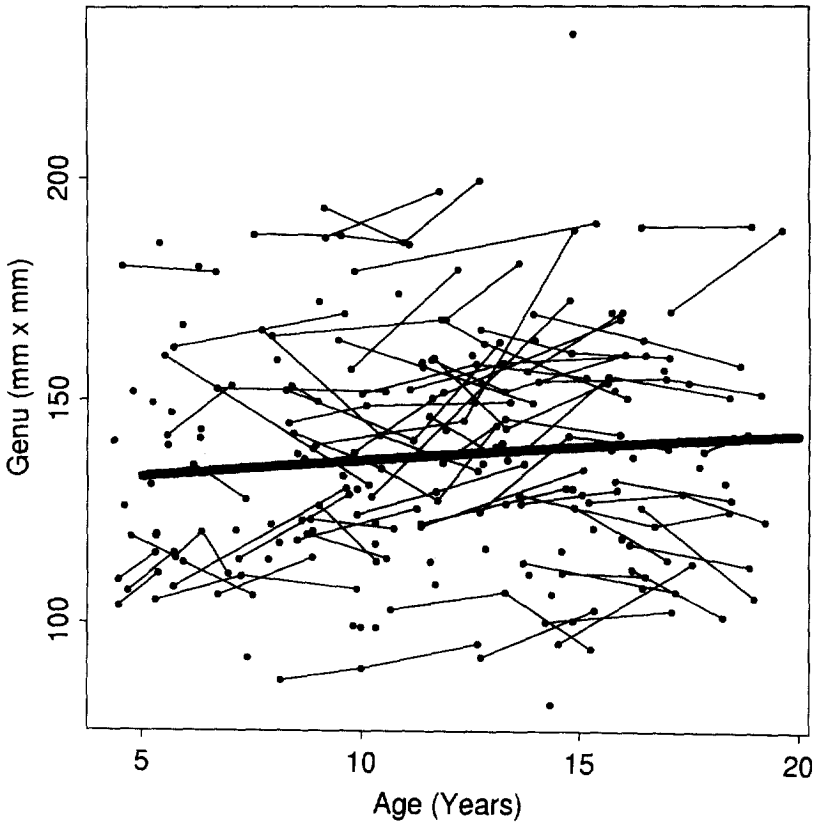

Fig 3. Scatterplots, with longitudinal data points connected by a line, of genu area (mm^2) vs age (years) for 251 scans from 139 healthy subjects ages 5 - 18 years.

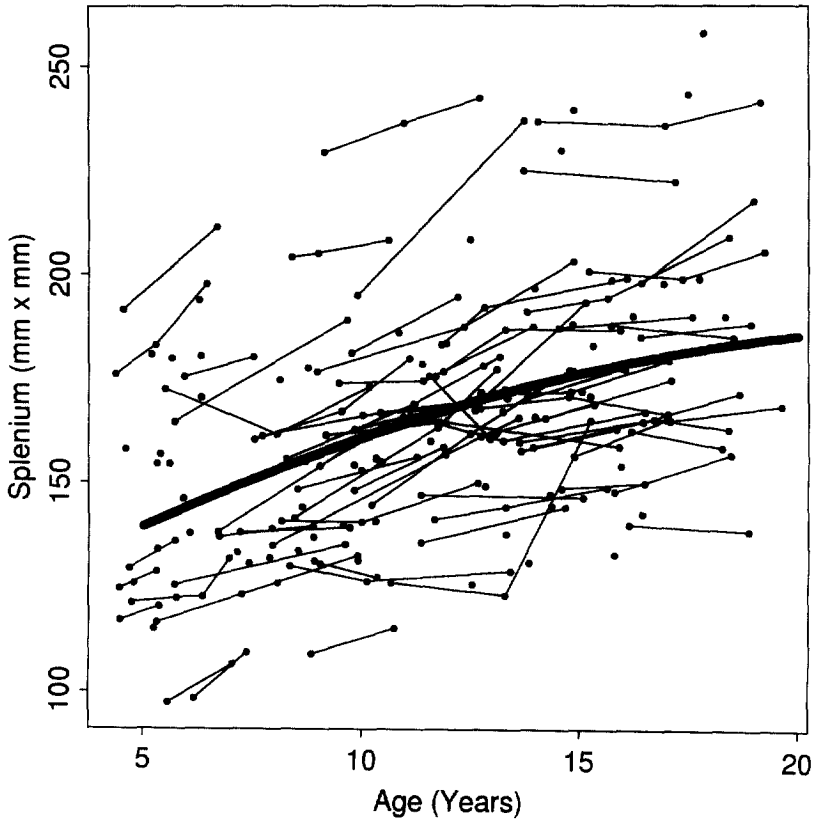

Fig 4. Scatterplots, with longitudinal data points connected by a line, of splenium size (mm^2) vs age (years) for 251 scans from 139 healthy subjects ages 5 - 18 years.

References

ACHENBACH, T.M. AND EDELBROCK, C.S. (1983) Manual for child behavior checklist and revised behavior profile. Department of Psychiatry, University of Vermont. Burlington, VT.

ANDREASEN, N.C., FLASHMAN, L., FLAUM, M., ARNDT, S., SWAYZE, V., 2ND, O'LEARY, D.S., EHRHARDT, J.C., AND YUH, W.T. (1994) Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA. 272, pp.1763-1769.

BAUMGARDNER, T.L., SINGER, H.S., DENCKLA, M.B., RUBIN, M.A., ABRAMS, M.T., COLLI, M.J., AND REISS, A.L. (1996) Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. Neurology. 47, pp.477-482.

BELL, A.D. AND VARIEND, S. (1985) Failure to demonstrate sexual dimorphism of the corpus callosum in childhood. J Anat. 143, pp.143-147.

BERLUCCHI, G. (1981) Interhemispheric asymmetries in visual discrimination: a neurophysiological hypothesis. Doc Opthal Proc Ser. 30, pp.87-93.

BIGELOW, L.H., NASRALLAH, H.A., AND RAUSCHER, F.P. (1983) Corpus callosum thickness in chronic schizophrenia. British Journal of Psychiatry. 142, pp.284-287.

BOGEN, J.E. AND BOGEN, G.M. (1969) The other side of the brain. Bull Los Ang Neurol Soc. 34, pp.73-220.

BYNE, W., BLEIER, R., AND HOUSTON, L. (1988) Variations in human corpus callosum do not predict gender: a study using magnetic resonance imaging. Behav Neurosci. 102, pp.222-227.

CASTELLANOS, F.X., GIEDD, J.N., MARSH, W.L., HAMBURGER, S.D., VAITUZIS, A.C., DICKSTEIN, D.P., SARFATTI, S.E., VAUSS, Y.C., SNELL, J.W., LANGE, N., KAYSEN, D., KRAIN, A.L., RITCHIE, G.F., RAJAPAKSE, J.C., AND RAPOPORT, J.L. (1996) Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch.Gen.Psychiatry. 53, pp.607-616.

CLARKE, S., KRAFTSIK, R., VAN DER LOOS, H., AND INNOCENTI, G.M. (1989) Forms and measures of adult and developing human corpus callosum: is there sexual dimorphism? Journal of Comparative Neurology. 280, pp.213-230.

CONNERS, C.K. (1973) Rating scales in drug studies with children. Psychopharmacol Bull. 24,

COOK, N.D. (1986) The brain code. Mechanisms of information transfer and the role of the corpus callosum. pp.255 Methuen. London.

COWELL, P.E., ALLEN, L.S., ZALATIMO, N.S., AND DENENBERG, V.H. (1992) A developmental study of sex and age interactions in the human corpus callosum. Developmental Brain Research. 66, pp.187-192.

DE LACOSTE, M.C., HOLLOWAY, R.L., AND WOODWARD, D.J. (1986) Sex differences in the fetal human corpus callosum. Human Neurobiology. 5, pp.93-96.

DE LACOSTE-UTAMSING, M.C. AND HOLLOWAY, R.L. (1982) Sexual dimorphism in the human corpus callosum. Science. 216, pp.1431-1432.

DENCKLA, M.B. (1985) Revised physical and neurological examination for subtle signs. Psychopharmacol Bull. 21, pp.773-800.

DIGGLE, P.J., LIANG, K.Y., AND ZEGER, S.L. (1994) Analysis of longitudinal data. Oxford University Press. Oxford.

FLEISCHHAUER, K. AND WARTENBERG, H. (1967) Elektonenmicroscopischen Untersuchungen uber das Wachstrum der Nervenfasern und uber das Auftreten von Mrkscheiden im Corpus Callosum der Katze. Z Zellforsch. 83, pp.568-581.

GIEDD, J.N., CASTELLANOS, F.X., CASEY, B.J., KOZUCH, P., KING, A.C., HAMBURGER, S.D., AND RAPOPORT, J.L. (1994) Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder [see comments]. Am. J. Psychiatry. 151, pp.665-669.

GIEDD, J.N., RUMSEY, J.M., CASTELLANOS, F.X., RAJAPAKSE, J.C., KAYSEN, D., VAITUZIS, A.C., VAUSS, Y.C., HAMBURGER, S.D., AND RAPOPORT, J.L. (1996a) A quantitative MRI study of the corpus callosum in children and adolescents. Brain Reseach: Developmental Brain Research. 91, pp.274-280.

GIEDD, J.N., SNELL, J.W., LANGE, N., RAJAPAKSE, J.C., KAYSEN, D., VAITUZIS, A.C., VAUSS, Y.C., HAMBURGER, S.D., KOZUCH, P.L., AND RAPOPORT, J.L. (1996b) Quantitative magnetic resonance imaging of human brain development: ages 4-18. Cerebral Cortex. 6, pp.551-560.

GOYETTE, C.H., CONNERS, C.K., AND ULRICH, R.F. (1978) Normative data on the Revised Conner's Parent and Teacher Rating Scales. J. Abnorm. Child Psychol. 6, pp.221-236.

HELLIGE, J.B., COX, J.P., AND LITVAC, L. (1979) Information processing in the hemispheres: selective hemisphere activation and capacity limitations. J Exp Psychol Gen. 108, pp.251-259.

HYND, G.W., SEMRUD-CLIKEMAN, M., LORYS, A.R., NOVEY, E.S., AND ELIOPULOS, D. (1990) Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. Arch. Neurol. 47, pp.919-926.

HYND, G.W., SEMRUD-CLIKEMAN, M., LORYS, A.R., NOVEY, E.S., ELIOPULOS, D., AND LYYTINEN, H. (1991) Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J. Learn. Disabil. 24, pp.141-146.

INNOCENTI, G.M., MANZONI, T., AND SPIDALIERI, G. (1974) Patterns of somesthetic messages transferred through the corpus callosum. Exp Brain Res. 19, pp.447-466.

INNOCENTI, G.M. AND CAMINITI, R. (1980) Postnatal shaping of callosal connections from sensory areas. Exp Brain Res. 38, pp.381-394.

INNOCENTI, G.M. (1981a) Growth and reshaping of axons in the establishment of visual callosal connections. Science. 218, pp.824-827.

INNOCENTI, G.M. (1981b) The development of interhemispheric connections. Trends in Neuroscience. 4, pp.142-144.

JACOBSEN, L.K., GIEDD, J.N., RAJAPAKSE, J.C., HAMBURGER, S.D., VAITUZIS, A.C., FRAZIER, J.A., LENANE, M.C., AND RAPOPORT, J.L. (1997) Quantitative magnetic resonance imaging of the corpus callosum in childhood onset schizophrenia. Psychiatry Res. 68, pp.77-86.

JOSEPH, R. (1980) Awareness, the origin of thought, and the role of conscious self-deception in resistance and repression. Psychol Rep. 46, pp.767-781.

JURASKA, J.M. AND KOPCIK, J.R. (1988) Sex and enviromental influences on the size and ultrastructure of the rat corpus callosum. Brain Research. 450, pp.1-8.

KAPPERS, C.U.A., HUBER, G.C., AND CROSBY, C.C. (1936) The comparative anatomy of the nervous system of vertebrates including man, Vol. 2. MacMillan co. New York.

LAMANTIA, A.S. AND RAKIC, P. (1984) The number, size, myelination, and regional variation of axons in the corpus callosum and anterior commissure of the developing rhesus monkey. Society for Neuroscience Abstracts. 10, pp.1081

LEVY, J. AND TREVARTHEN, C. (1981) Color-matching, color naming and color memory in split brain patients. Neuropsychol. 19, pp.523-541.

LEVY, J. (1985) Interhemispheric collaboration: single mindedness in the asymmetric brain. pp.11-32. Academic Press. New York.

MALOBABIC, S., SIMIC, S., AND MARINKOVIC, S. (1985) Significance of the encephalometric parameters of human corpus callosum and medial hemispheric surface. Anat Anz Jena. 159, pp.231-239.

NASRALLAH, H.A., SHARMA, S., AND OLSON, S.C. (1997) The volume of the entorhinal cortex in schizophrenia: A controlled MRI study. Progress In Neuro-Psychopharmacology & Biological Psychiatry. 21, pp.1317-1322.

NJIOKIKTJIEN, C. (1991) Pediatric Behavioral Neurology, Vol.3, The Child's Corpus Callosum. pp.22 Suyi Publications. Amsterdam.

OPPENHEIM, J.S., BENJAMIN, A.B., LEE, C.P., NASS, R., AND GAZZIANGA, M.S. (1987) No sex-related differences in human corpus callosum based on magnetic resonance imagery. Annals of Neurology. 21, pp.604-606.

PARASHOS, I.A., WILKINSON, W.E., AND COFFEY, C.E. (1995) Magnetic resonance imaging of the corpus callosum: predictors of size in normal adults. Journal of Neuropsychiatry. 7, pp.35-41.

PETERSON, B.S., LECKMAN, J.F., DUNCAN, J.S., WETZLES, R., AND RIDDLE, M.A. (1994) Corpus callosum morphology from magnetic resonance images in Tourette's syndrome. Psychiatry Research: Neuroimaging. 55, pp.85-99.

RAPOPORT, S.I. (1990) Integrated phylogeny of the primate brain, with special reference to humans and their diseases. Brain Resarch Reviews. 15, pp.267-294.

RASBAND, W. (1993) Image (1.6). National Institues of Health (Public Domain). Bethesda, MD.

ROSENTHAL, R. AND BIGELOW, L. (1972) Quantitative brain measurements in chronic schizophrenia. British Journal of Psychiatry. 121, pp.259-264.

SAS INSTITUTE. (1990) SAS, version 6. SAS Institutes, Inc. Cary, North Carolina.

SEMRUD-CLIKEMAN, M., FILIPEK, P.A., BIEDERMAN, J., STEINGARD, R., KENNEDY, D., RENSHAW, P., AND BEKKEN, K. (1994) Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry. 33, pp.875-881.

SHANKS, M.F., ROCKEL, A.J., AND POWEL, T.P.S. (1975) The commissural fiber connections of the primary somatic sensory cortex. Brain Res. 98, pp.166-171.

SNELL, J.W., MERICKEL, M.B., ORTEGA, J.M., GOBLE, J.C., BROOKEMAN, J.R., AND KASSELL, N.F. (1995) Model-based boundary estimation of complex objects using hierarchical active surface templates. Pattern Recognition. 28, pp.1599-1609.

SPIDALIERI, G., FRANCHI, G., AND GUANDALINI, P. (1985) Somatic receptive-field properties of single fibers in the rostral portion of the corpus callosum in awake cats. Exp Brain Res. 58, pp.75-81.

TOMASCH, J. (1954) Size, distribution and number of fibers in the human corpus callosum. Anat Rec. 119, pp.119-135.

WAXMAN, S.G. AND SWADLOW, H.A. (1976) Ultrastructure of visual callosal axons in the rabbit. Exp Neurol. 53, pp.115-128.

WECHSLER, D. (1974) Wechsler intelligence scale for children - revised. The Psychological Corporation. New York.

WEIS, S., WEBER, G., WENGER, E., AND KIMBACHER, M. (1988) The human corpus callosum and the controversy about sexual dimorphism. Psychobiol. 16, pp.411-415.

WEIS, S., WEBER, G., WENGER, E., AND KIMBACHER, M. (1989) The controversy about sexual dimorphism of the human corpus callosum. Int J Neurosci. 47, pp.169-173.

WELNER, Z., REICH, W., HERJANIC, B., JUNG, K., AND AMADO, H. (1987) Reliability, validity and child agreement studies of the diagnostic interview of children and adolescents (DICA). J. Amer. Acad. Child Adol. Psychiat. 26, pp.649-653.

WITELSON, S.F. (1985a) The brain connection: the corpus callosum is larger in left-handers. Science. 229, pp.665-668.

WITELSON, S.F. (1985b) On hemisphere specialization and cerebral plasticity from birth. pp.33-85. Acad Press Inc. Orlando.

WITELSON, S.F. (1989) Hand and Sex Differences in the Isthmus and Genu of the Human Corpus Callsoum. Brain. 112, pp.799-835.

ZAIDEL, D. AND SPERRY, R.W. (1974) Memory impairment after commissurotomy in man. Brain. 97, pp.263-272.

ZAIDEL, D. AND SPERRY, R.W. (1977) Some long-term effects of cerebral commissurotomy in man. Neuropsychol. 15, pp.193-204.

Inquiries and reprint requests should be addressed to:

Jay N. Giedd, M.D.
National Institute of Mental Health
Child Psychiatry Branch
Building 10, Room 4C110
10 Center Drive, MSC 1367
Bethesda, Maryland 20892
Phone: (301) 435-4517
Fax: (301) 480-8898
Email: jgiedd@helix.nih.gov